FEB - 5 2004

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

Device Name	**QCA** (Version 3.1) A videomicroscopy software system for quantitative estrogen receptor immunohistochemistry
Common Name	Digital analyzer
510(k) Number	**k031363**
Classification	A new class II in vitro medical device MYA Hematology: Immunohistochemistry Antibody Assay, Estrogen Receptor 21 CFR 864.1860
Applicant	Cell Analysis, Inc 1801 Maple Avenue Evanston, Il 60201 United States of America
Applicant Contact	Joel Herm President 866-235-5442 joel.herm@cellanalysis.com
Manufacturer (single site)	Cell Analysis, Inc. 1801 Maple Avenue Evanston, Il 60201 United States of America Device Establishment Registration Number: 9052602
Predicate Device	Modification to ACIS (Automated Cellular Imaging System) k012138, September 30, 2002 ChromaVision Medical Systems, Inc. Capestrano, CA
Submission Date	May 29, 2003

Summary narrative

Immunohistochemistry special stains are often used by pathologists for many purposes. However, there is a need for objectivity in the assessment of such stains, as manual observation by individual pathologists suffers from subjectivity and inter-observer variability. With this need in mind, Cell Analysis, Inc. was founded to develop a quantitative cellular image analysis system entitled QCA. It is specifically designed to help pathologists make objective measurements of the estrogen receptor nuclear antigens visualized by immunohistochemistry (IHC). The system is essentially software that analyzes images captured by a pathologist through a video camera using the pathologist's own microscope and desktop computer. The system requires competent human intervention at all steps in the analysis process. After the pathologist chooses appropriate fields for analysis, enters necessary settings, and masks areas of non-tumor if desired, the system will automatically derive an overall score of the field of interest. Should the pathologist disagree with the score, s/he can adjust QCA settings so that the system derives a score that matches their professional assessment.

To determine substantial equivalence of the system to a predicate, QCA was compared against the stand-alone ChromaVision imaging system (ACIS) and against manual assessment by highly trained pathologists. The ChromaVision ACIS system constitutes an FDA-cleared Class II medical device with an almost identical intended use as Cell Analysis' QCA system. However, it should be understood that manual inspection of immunohistochemistry special stains remains the method of choice for this analysis in the vast majority of all pathology laboratories, and must therefore be considered the standard to which other systems should be compared.

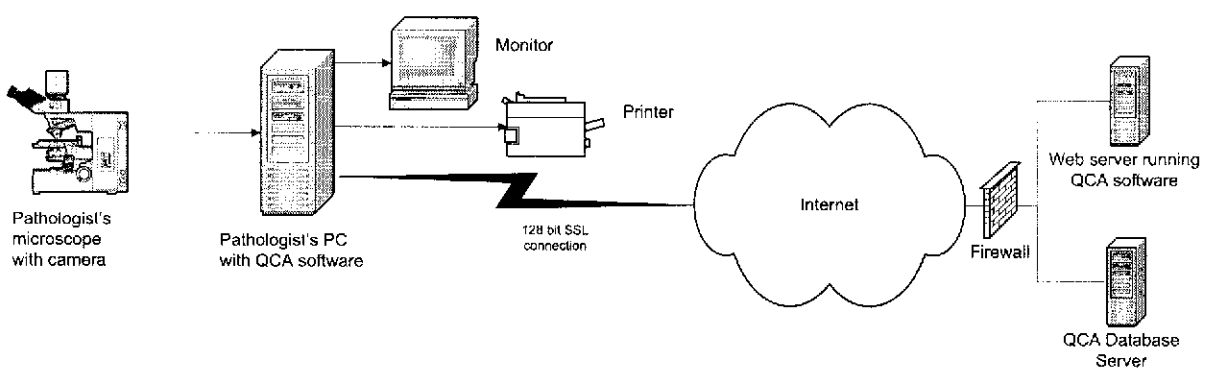
The Cell Analysis QCA system is designed to analyze the estrogen receptor (ER) antigen, and for test purposes 32 breast cancers were chosen from archival material at Lake Forest Hospital and stained immunohistochemically for ER. Each of these 32 slides (and appropriate control slides) was analyzed by the Cell Analysis QCA system, the ChromaVision ACIS system, and manually by three highly trained pathologists. All assessments and analyses were made in blinded fashion. The correlations between the individual pathologists' manual results and the QCA results were all excellent.

Legally marketed predicate device and method to which substantial equivalence is claimed - 807.92(a)(3)

> *Digital analyzer:* ChromaVision Medical Systems, Inc's ACIS (Automated Cellular Imaging System) for detection of ER/PR found to be substantially equivalent on September 30, 2002 (kO12138)

Description of the device - 807.92(a)(4)

QCA is a standalone, automated intelligent cell assessment software device that analyzes digital images of cells of interest by pixel color attributes and pixel area detection algorithms. The software system utilizes a pathologist's own personal computer, light microscope, digital camera, printer, and Internet connection.



Intended Use - 807.92(a)(5)

The QCA device is intended to detect and classify cells of clinical interest based on recognition of cellular areas of particular color and chromatic intensity. In this software application, the QCA device is intended to measure and quantitate the percentage and intensity of positively stained nuclei in formalin-fixed, paraffin-embedded tissue specimens immunohistochemically stained for estrogen receptors.

It is indicated for use as an aid in the management, prognosis and prediction of therapy outcomes of breast cancer when used with reagents validated for those indications.

The QCA system is an adjunctive computer-assisted methodology to assist the reproducibility of a qualified pathologist in the acquisition and measurement of images from microscopic slides of breast cancer specimens stained for the presence of estrogen (ER) nuclear receptor protein. The accuracy of the test result depends upon the quality of immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls to assure the validity of the QCA ER scores.

Technological characteristics - 807.92(a)(6)

The method of cell assessment is similar to the predicate device; i.e., colorimetric pattern recognition by microscopic examination of digital images of prepared cells by chroma (hue and intensity), and histologic area as observed by a pathologist-controlled microscope/digital camera combination. Assessment algorithms have been designed to mimic visual observations by highly trained health care professionals.

Non-clinical Study Outline

- 32 invasive breast carcinoma tissue specimens with a range of ER positivity/negativity were selected from different patients.
- Tissue blocks were sent to an outside CLIA-approved lab
- Outside lab performed IHC for ER on all 32 cases following predicate device's specifications
- Outside lab pathologists used predicate device to derive percent positivity.
- Predicate device results were kept blind
- Outside lab returns all 32 IHC slides to Cell Analysis.
- Based on professional judgment acquired through pathology training and experience, two pathologists captured 3 representative images from each case (2 * 3 * 32 = 192)
- Three different pathologists performed independent manual inspection and derived scores for 192 randomly mixed images
- Manual inspection results were kept blind
- One of the three above-mentioned pathologists used the candidate device (QCA) to analyze the same 192 images without manually overriding the program's scores
- All results were un-blinded and data from predicate device, manual inspections, and QCA were compared

Performance Characteristics

For all comparison studies the primary estrogen receptor antibody used was the DakoCytomation 1D5 clone (FDA 510(K) cleared). The detection system was the labeled Streptavidin-Biotin peroxidase system (LSAB2), also purchased from DakoCytomation Corporation. Please see Appendix on page 9 of this Summary for the immunohistochemistry staining protocol used in all studies of this submission.

QCA ER Percent Positivity vs. Manual Percent Positivity Evaluation

Manual evaluation: As manual inspection of IHC slides remains the most widely utilized method by a wide margin*, therefore this must be considered the standard of current pathology practice. However, it is also recognized that manual inspection suffers from considerable inter-observer variability.

QCA chose tissue specimens from 32 consecutive invasive breast cancers received in a pathology practice over a three and a half month period. Based on professional judgment, three representative images of each ER slide were digitally captured by each of two pathologists. These 192 different images (3 images x 2 pathologists x 32 cases = 192 images) were then first randomly mixed and then screened by each of three different pathologists to ensure blinding of results. The three then manually assessed the percentage of tumor cell nuclei with weak positive ER IHC staining (% weak positivity), the percentage of tumor cell nuclei with moderate positive staining (% moderate positivity), and the percentage of tumor cell nuclei with strong staining (% strong positivity) for each slide. From these determinations, a total percentage of tumor cell nuclei with any degree of positivity (% total positivity) was calculated for each slide.

(% total positivity) = (% weak positivity) + (% moderate positivity) + (% strong positivity)

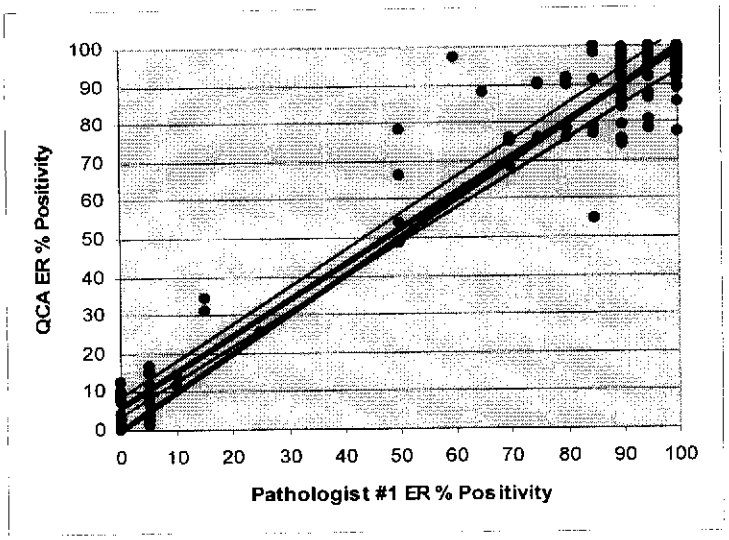
A completely ER-negative tumor was scored as 0%, and a tumor showing any degree of positive ER staining of all tumor cells (regardless whether the staining is weak, moderate, or strong) was scored as 100%.

QCA evaluation: The same 192 images were then assessed with the QCA software by one pathologist without any manual adjustments of the nuclear thresholds. The pathologist did mask nine of the images to exclude areas of non-tumorous cells.

Different from the manual study, instead of counting the percent of positively stained nuclei, QCA software evaluates individual "nuclear pixels" and automatically assigns a staining intensity score 0, 1, 2, or 3 to each pixel. Each pixel's individual score is automatically determined based on the negative control and positive control provided by the pathologist at the beginning of the testing. Any degree of staining above the negative control will be assigned by QCA as a "positive" pixel. QCA will calculate the "% weak positivity" (as the number of weakly stained pixels against the total number of nuclear pixels), % moderate positivity, and % strong positivity. Using the same formula, the total percent of positively stained pixels (% total positivity) can be calculated as follows: (% total positivity) = (% weak positivity) + (% moderate positivity) + (% strong positivity).

Regression analysis was performed by using individual pathologist's (manually assessed positively stained nuclei) manual ER percent positivity against QCA's (nuclear pixel) ER percent positivity. The results of three pathologists are shown on the next page.

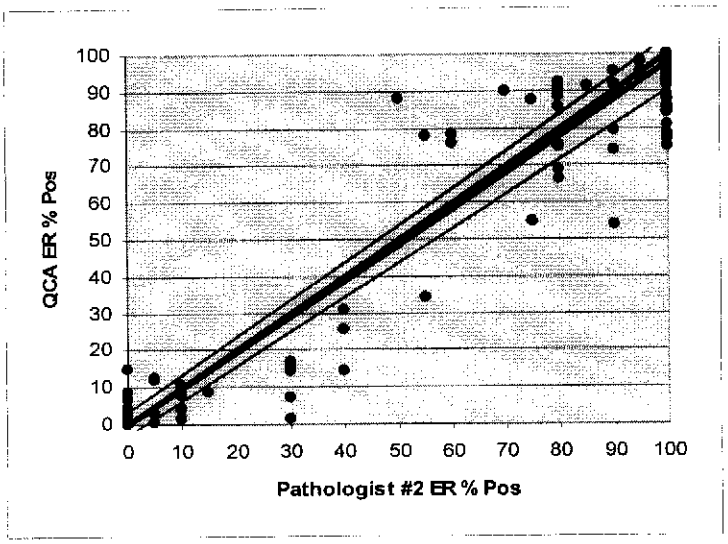
* Layfield LJ, Gupta D, Mooney EE. _ Assessment of Tissue Estrogen and Progesterone Receptor Levels: A Survey of Current Practice, Techniques, and Quantitation Methods. *Breast J. 2000; 6:189-196.*



Regression line
95% confidence level
X = Y

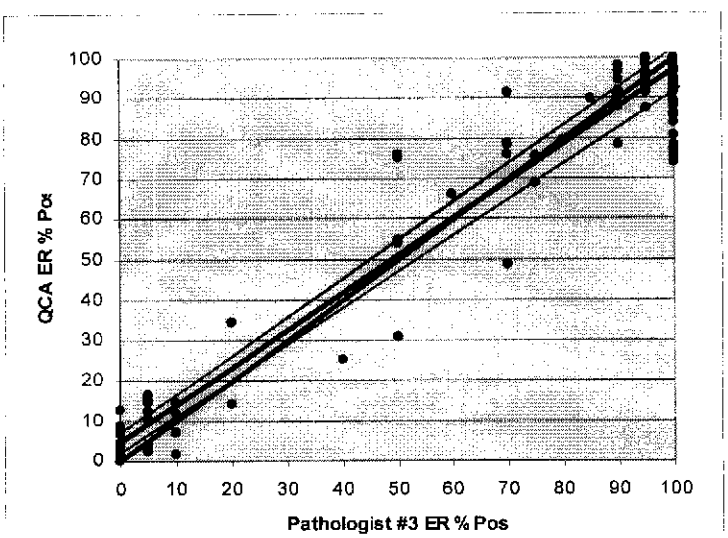
Pathologist #1

Corr Coef (R) =0.957
Slope = 0.92
Intercept = 6.18
SE of regression line = 7.09
N=192



Pathologist #2

Corr Coef (R) =0.934
Slope = 0.97
Intercept = 0.15
SE of regression line = 8.81
N=192

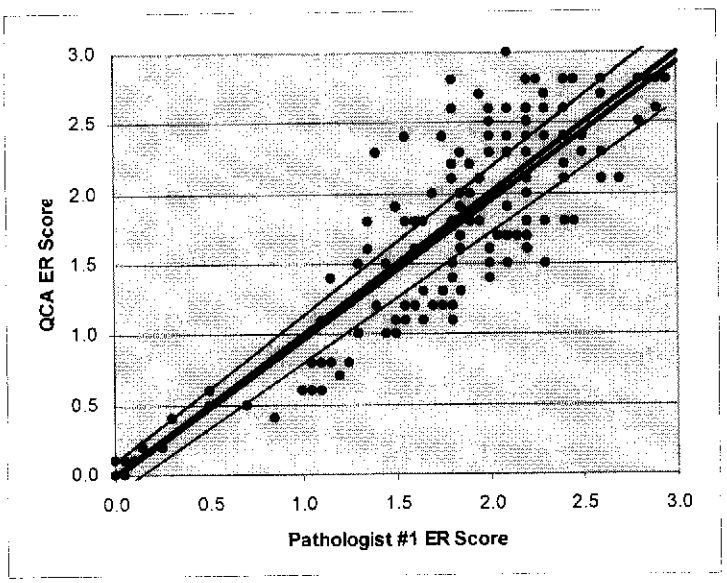


Pathologist #3

Corr Coef (R) =0.925
Slope = 0.92
Intercept = 4.62
SE of regression line = 7.36
N=192

QCA ER Score vs. Manual Score Evaluation

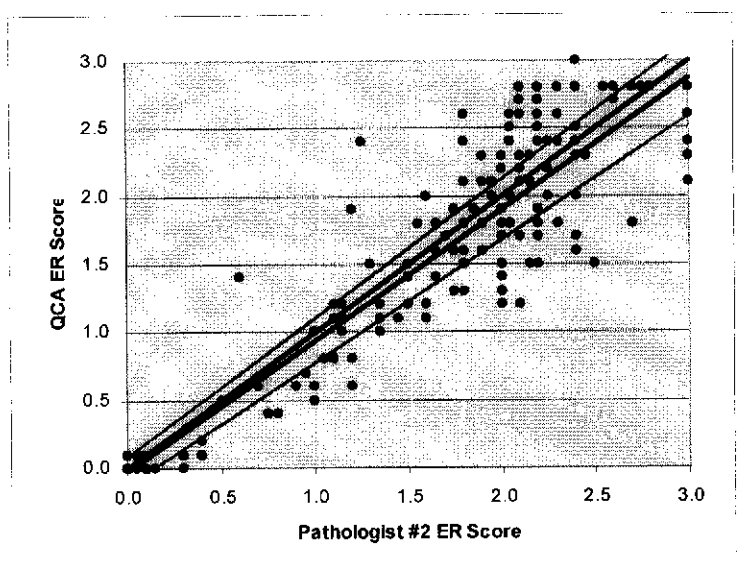
Using the same 32 consecutive invasive breast cancer slides mentioned in the outline, a different scoring system that additionally incorporates the intensity of the ER staining, the intensity score, was also generated by the same manual inspection method (Manual ER Score) and by QCA software (QCA ER Score). Both manual and QCA scores were calculated using the same formula: Intensity Score ={(% weak positivity x 1) + (% moderate positivity x 2) + (% strong positivity x 3)} / 100%. As mentioned above, the manual score is nuclei based and QCA is pixel based. This Intensity Score is adopted and modified from the concept of HSCORE*, which is currently used in many pathology laboratories for ER scoring.



Regression line
95% confidence level
X = Y

Pathologist #1

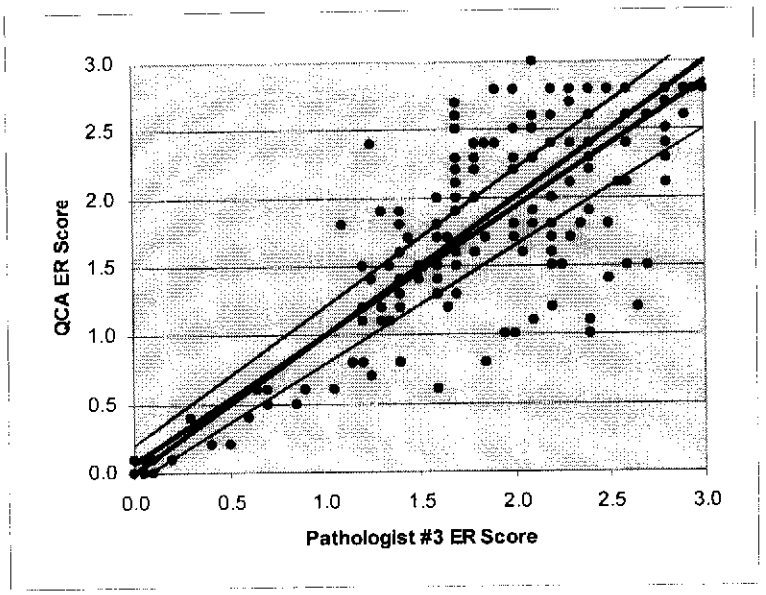
Corr Coef (R) =0.849
Slope = 0.98
Intercept = -0.01
SE of regression line = 0.37
N=192



Pathologist #2

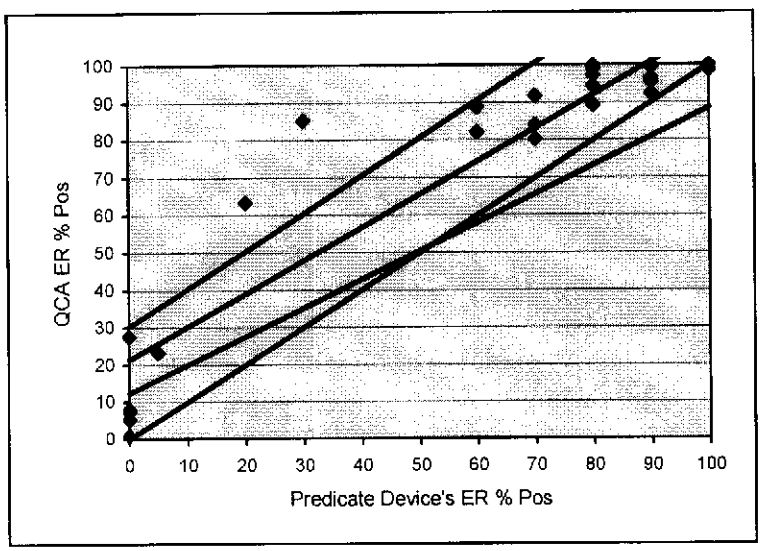
Corr Coef (R) =0.854
Slope = 0.92
Intercept = -0.02
SE of regression line = 0.36
N=192

* HSCORE = Σ (I + 1) × PC, where I and PC represent the intensity and the percentage of cells that stained at each positive intensity category, respectively. (McCarty KS Jr.. et al. Cancer Res. 1986;46(8 Suppl):4244s-4248s.)



QCA ER Percent Positivity vs. Predicate Device ER Percent Positivity Evaluation

We performed regression analysis comparing the predicate device results to those of QCA for percent positivity. The predicate device's percent positivity values on 32 cases were provided by a CLIA-approved laboratory on a case-by-case (slide-by-slide) basis only. The values were provided in 10% increments on 31 cases, one case was reported at 5% . The QCA percent positivity was the cumulative assessment by QCA of all 6 images taken of each of the same 32 cases. The following figure shows the regression results of the predicate device's ER percent positivity against QCA's ER percent positivity. The regression statistics are shown in the legend.



Regression line
95% confidence level
X = Y

Corr Coef (R) =0.897
Slope = 0.88
Intercept = 21.3
SE of regression line = 11.8
n = 32

Qualitative Percent Positivity Comparison Study

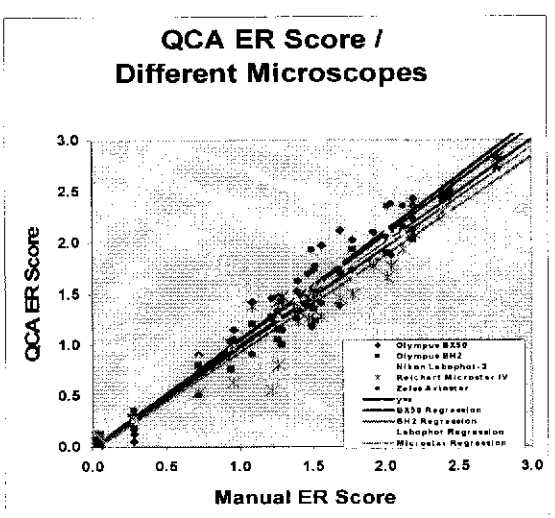
The following agreement tables include the data from the original 32 invasive breast carcinomas (as described in the Outline, page 3 of the Summary, 6 images taken per case/slide) and an additional 120 cases (4 images per case/slide according to our determination of the optimum number of images to consider per case study). These cases include both invasive and in-situ breast cancers that were processed and stained according to the protocol listed in the Appendix. The QCA final percent positivity for each of the 152 (32 + 120) cases/slides was calculated based on the cumulative assessment of all tumor cell nuclear pixels taken from each case (see QCA Evaluation, page 4 above). The manual percent positivity for each of the 152 total cases was calculated based on the same formula shown on page 4 (manual evaluation). Interpretations of **positive** breast tumor **ER status** vary from 1% to 10% of percent positivity in different pathology laboratories (see reference by Layfield LJ. page 4). We used ≥5.0% and ≥1.0% positivity as example cut-off values, and derived the following qualitative agreement tables to compare the manual against the QCA methods.

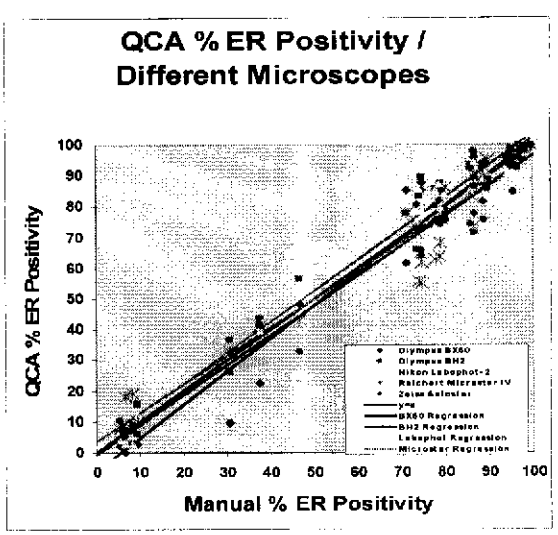
1.0%≥Positive		Manual	
		Positive	Negative
QCA	Positive	**149**	**0**
	Negative	**0**	**3**

5.0% ≥ Positive		Manual	
		Positive	Negative
QCA	Positive	**136**	**2**
	Negative	**2**	**12**

Inter-microscope Variability Study

The QCA system was installed in 5 different pathologists' offices, one with an Olympus BX50 microscope, another with an Olympus BH-2 microscope, another with a Nikon Labophot-2 microscope, another with a Reichert Micro Star IV microscope, and the last with a Zeiss Axiostar Plus microscope. Having previously shown that four images per case yield results within one standard deviation of the true mean for QCA score and percent positivity, four images of each of the 32 breast cancers were captured and analyzed on each of the five systems. For each case, appropriate negative and positive controls were also captured. As described on page 4 (QCA evaluation), the final QCA score and percent positivity for each case/slide is the cumulative average of 4 images taken for each case. The next two figures show the regression results of QCA ER score and QCA percent positivity against those of the manual results.





Inter-microscope Variability Study Data

	BX50		BH2		Labophot		Microstar		Axiostar	
	%Pos	Score	%Pos	Score	%Pos	Score	%Pos	Score	%Pos	Score
n	32	32	32	32	32	32	32	32	32	32
Corr Coef	0.976	0.980	0.988	0.989	0.982	0.980	0.964	0.962	0.980	0.977
Slope (m)	1.081	1.065	1.018	0.984	0.999	0.963	0.930	0.952	0.972	1.037
m low 95%	0.991	0.983	0.959	0.929	0.927	0.891	0.834	0.852	0.899	0.953
m high 95%	1.171	1.146	1.077	1.038	1.071	1.035	1.026	1.053	1.046	1.121
Intercept (b)	-6.125	-0.015	1.634	-0.016	1.831	0.058	3.481	-0.027	-0.822	0.001
b low 95%	-13.134	-0.142	-2.969	-0.101	-3.830	-0.054	-4.042	-0.183	-6.553	-0.129
b high 95%	0.884	0.111	6.237	0.068	7.492	0.170	11.005	0.128	4.910	0.131
SE	7.331	0.169	4.814	0.113	5.920	0.150	7.868	0.209	5.994	0.174

QCA Within-Image Reproducibility Study

To document the within-image reproducibility of the QCA system, ten different breast cancer cases/slides that had been subjected to the same ER antibody staining protocol (as mentioned below in the Appendix) were chosen to perform the following reproducibility study.

An individual microscopic field from each of ten different slides was repeatedly captured 10 times using the QCA system. Every result within each set of 10 images was absolutely identical with respect to QCA ER score and percentage positivity (data not shown). This experimental design tested the reproducibility of the microscope/camera systems as well as that of the software itself.

Performance Data Conclusions

The QCA system provided an objective measure at least equal to the manual inspection of the individual pathologists and was substantially equivalent to the predicate device.

Appendix:

The immunohistochemistry staining procedure used in all studies for this submission.

1. Formalin-fixed, paraffin-embedded breast tumor tissue blocks were sectioned at 5 microns in thickness.
2. These tissue sections were affixed onto glass slides by baking in a dry oven at 60°C for 30 minutes.
3. The slides were de-paraffinized through xylene and hydrated through 100%, 95% and 70% ethyl alcohol then finally in distilled water.
4. Antigen retrieval was achieved by immersing slides in a jar with 1mM EDTA pH7.5 solution. This jar was placed in a steamer and steamed for 30 minutes. It was then allowed to cool for 20 minutes.
5. Slides were immersed in 3% hydrogen peroxide and protein blocking solution (DakoCytomation) for 10 minutes each to block the non-specific antigen binding sites and to neutralize the endogenous peroxidase activity.
6. The slides were incubated with DakoCytomation 1D5 ER monoclonal antibody (1/25 dilution) at room temperature for 30 minutes.
7. These slides were then incubated with biotinylated secondary antibody for 30 minutes
8. The slides were then incubated with streptavidin-horseradish peroxidase conjugate for 30 mintures
9. 3.3' diamino-benzidine (DAB) Chromogen was added and allowed to develop color for 5 mintutes.
10. The slides were counter-stained with Gill 3 hematoxylin for 5 minutes.
11. Slides were dehydrated and coverslipped.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

FEB - 5 2004

Mr. Joel Herm
President
Cell Analysis, Inc.
1801 Maple Avenue
Suite 2319
Evanston, Illinois 60201-3135

Re: k031363
Trade/Device Name: QCA (Quantitative Cellular Assessment)
Regulation Number: 21 CFR § 864.1860
Regulation Name: Immunohistochemistry reagents and Kits
Regulatory Class: II
Product Code: NQN
Dated: November 6, 2003
Received: November 10, 2003

Dear Mr. Herm:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 594-3084. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Joseph L. Hackett, Ph.D.
Acting Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

510(k) Number: k031363

Device Name: QCA

Indications for Use

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Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K031363

(Please do not write below this line – Continue on another page if necessary)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ **Or** **Over-the-Counter Use** _____
(Per 21 CFR 801.109)